AD_____

MIPR NO: 95MM5515

TITLE: Influence of parenteral progesterone administration on the prevalence and severity of mastodynia in active duty servicewomen: a multi-institutional cross-sectional study.

PRINCIPAL INVESTIGATOR: David M. Euhus, MD, MAJ, MC

CONTRACTING ORGANIZATION: Tripler Army Medical Center
Tripler Army Medical Center, Hawaii
96859-5000

REPORT DATE: 1 SEP 1995

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	1 SEP 1995	Annual 15 Nov 94 - 1 Aug 95

4. TITLE AND SUBTITLE
Influence of Parenteral Progesterone Administration on the Prevalence and Severity of Mastodynia in Active Duty Servicewomen: A Multi-Institutional Case-Control Study

5. FUNDING NUMBERS
95MM5515

6. AUTHOR(S)
David M. Euhus, MAJ

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Tripler Army Medical Center
Tripler Army Medical Center, Hawaii 96859-5000

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

Breast pain (mastodynia) afflicts more than 30% of women attending surgical breast clinics. The pain can be quite severe and may impair job performance and interpersonal relationships. The use of progesterones in the treatment of mastodynia remains controversial, but commonly practiced in some settings. The literature supporting this approach is inconclusive because the studies typically involve only small numbers of patients and are generally uncontrolled. In addition, questions of medication compliance are never addressed. This study employs a validated survey instrument and a cross sectional design to assess the prevalence and severity of mastodynia in a large cohort of women receiving long acting parenteral progesterones and in an even larger group of age-matched controls. At the time of this writing, 11 gynecology and family practice clinics have obtained human use approval and are actively enrolling patients. Thus far, 1,300 patients have been enrolled, and 533 have returned completed questionnaires. Control arm accrual is currently underway as well, and, at the time of this writing, questionnaires have been mailed to 3,449 randomly selected, age-matched controls. Detailed analysis of the data generated by this study will provide an accurate measure of the prevalence of mastodynia among active duty service women, assess attitudes about medical care for mastodynia and either support or refute a role for progesterones in the prevention and treatment of this common condition.

14. SUBJECT TERMS
DTIC QUALITY INSPECTED 5
Mastodynia, Progesterone, Depo-Provera, Survey

15. NUMBER OF PAGES
7

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

GENERAL INSTRUCTIONS FOR COMPLETING SF 298

The Report Documentation Page (RDP) is used in announcing and cataloging reports. It is important that this information be consistent with the rest of the report, particularly the cover and title page. Instructions for filling in each block of the form follow. It is important to ***stay within the lines*** to meet ***optical scanning requirements***.

Block 1. Agency Use Only *(Leave blank)*.

Block 2. Report Date. Full publication date including day, month, and year, if available (e.g. 1 Jan 88). Must cite at least the year.

Block 3. Type of Report and Dates Covered. State whether report is interim, final, etc. If applicable, enter inclusive report dates (e.g. 10 Jun 87 - 30 Jun 88).

Block 4. Title and Subtitle. A title is taken from the part of the report that provides the most meaningful and complete information. When a report is prepared in more than one volume, repeat the primary title, add volume number, and include subtitle for the specific volume. On classified documents enter the title classification in parentheses.

Block 5. Funding Numbers. To include contract and grant numbers; may include program element number(s), project number(s), task number(s), and work unit number(s). Use the following labels:

C	- Contract	**PR**	- Project
G	- Grant	**TA**	- Task
PE	- Program Element	**WU**	- Work Unit Accession No.

Block 6. Author(s). Name(s) of person(s) responsible for writing the report, performing the research, or credited with the content of the report. If editor or compiler, this should follow the name(s).

Block 7. Performing Organization Name(s) and Address(es). Self-explanatory.

Block 8. Performing Organization Report Number. Enter the unique alphanumeric report number(s) assigned by the organization performing the report.

Block 9. Sponsoring/Monitoring Agency Name(s) and Address(es). Self-explanatory.

Block 10. Sponsoring/Monitoring Agency Report Number. *(If known)*

Block 11. Supplementary Notes. Enter information not included elsewhere such as: Prepared in cooperation with...; Trans. of...; To be published in.... When a report is revised, include a statement whether the new report supersedes or supplements the older report.

Block 12a. Distribution/Availability Statement. Denotes public availability or limitations. Cite any availability to the public. Enter additional limitations or special markings in all capitals (e.g. NOFORN, REL, ITAR).

- **DOD** - See DoDD 5230.24, "Distribution Statements on Technical Documents."
- **DOE** - See authorities.
- **NASA** - See Handbook NHB 2200.2.
- **NTIS** - Leave blank.

Block 12b. Distribution Code.

- **DOD** - Leave blank.
- **DOE** - Enter DOE distribution categories from the Standard Distribution for Unclassified Scientific and Technical Reports.
- **NASA** - Leave blank.
- **NTIS** - Leave blank.

Block 13. Abstract. Include a brief *(Maximum 200 words)* factual summary of the most significant information contained in the report.

Block 14. Subject Terms. Keywords or phrases identifying major subjects in the report.

Block 15. Number of Pages. Enter the total number of pages.

Block 16. Price Code. Enter appropriate price code *(NTIS only)*.

Blocks 17. - 19. Security Classifications. Self-explanatory. Enter U.S. Security Classification in accordance with U.S. Security Regulations (i.e., UNCLASSIFIED). If form contains classified information, stamp classification on the top and bottom of the page.

Block 20. Limitation of Abstract. This block must be completed to assign a limitation to the abstract. Enter either UL (unlimited) or SAR (same as report). An entry in this block is necessary if the abstract is to be limited. If blank, the abstract is assumed to be unlimited.

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the US Army.

____ Where copyrighted material is quoted, permission has been obtained to use such material.

____ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

DME Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

____ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

DME For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

David M McCann 3 May 95

PI - Signature Date

TABLE OF CONTENTS

INTRODUCTION

Approximately 30% of women presenting to surgical breast clinics present for symptoms of breast pain[1]. While approximately 85% of these women are adequately managed by reassurance after a thorough evaluation, 15% will find that the breast pain poses intolerable life-style limitations[2]. Therapies for intractable mastodynia are generally directed at altering the hormonal milieu of the breast, but none is completely reliable and all are currently under close scrutiny.

The specific physiologic and mechanical causes of breast pain are unclear at this time. A growing body of literature, however, suggests that excess estrogen **effect** at the level of the breast ductules and lobules is a central feature. Estrogen is produced by a maturing ovarian follicle each month. The corpus luteum, which remains after rupture of the follicle, produces progesterone during the later half of the cycle. Estrogen stimulates proliferation of the ductal epithelial cells, while progesterone stimulates differentiation of the lobules. Estrogen drives the proliferative response, while progesterone organizes and subdues it. It has been postulated that when this delicate balance shifts towards a relative estrogen excess, breast pain and nodularity results.

As a group, patients with benign breast disease have higher estrogen/progesterone ratios in their sera than women without symptoms of breast disease[3]. While this alteration is sometimes the result of an absolute estrogen excess[4,5], it more frequently represents diminished progesterone levels (so called "luteal insufficiency")[6,7,8].

Progesterone administration represents a very direct way to shift the estrogen/progesterone ratio in favor of progesterone. Physiologic and biochemical effects of progesterone include inhibition of ovarian steroidogenesis through gonadotropin blockade, decreased estrogen receptor synthesis, increased estrogen degradation and improved translocation of the progesterone receptor into the nucleus.

One of the earliest trials of progesterone in the treatment of benign breast disease demonstrated symptomatic improvement in 96% of 234 women with mastodynia[9,10]. In this uncontrolled study, a total of 260 women with various forms of benign breast disease were treated with topical progesterone cream and oral Lynestrenol (3-deoxy-17-ethynyl-nortestosterone) at 10 mg per day on days 10 - 25 of the menstrual cycle. Symptomatic improvement was correlated with a decrease in breast nodularity on palpation, but no improvement in the mammographic appearance of the breasts. A second, smaller Lynestrenol trial also demonstrated symptomatic improvement in 96% of 26 women with

mastodynia[11]. A recent uncontrolled trial comparing lynestrenol with two dosage levels of a more potent progesterone (promegestone) found a 92.4% improvement rate in the lynestrenol group[12]. The promegestone group experience a similar improvement rate. The only placebo-controlled trial of this drug, however, included 160 patients and recorded an 82.1% symptomatic improvement rate in the treatment arm as compared to 36.8% in the placebo arm[13].

A variety of progesterone medications have been evaluated for the treatment of mastodynia. Among these is a progesterone ointment which was popularized in France. While an uncontrolled trial demonstrated improvement in 87% of 52 patients[14], a double-blind, placebo-controlled, cross-over trial involving 25 patients failed to document any effect[15]. In contrast, treatment with a 2.5% progesterone vaginal cream resulted in a >50% reduction in analog pain scale scores in 64.9% of 40 treatment arm patients as compared to 22.2% of a placebo arm ($P<0.01$)[16].

The most commonly prescribed progestagenic medication in the United States is medroxyprogesterone acetate (Provera®). This agent was assessed in a small (N = 18 evaluable patients) randomized prospective trial and found to be ineffective for mastodynia when administered in a dose of 10 mg per day on days 10 - 26 of the menstrual cycle[17].

The literature describing progesterone supplementation for the treatment of mastodynia is confusing. The studies are generally small and uncontrolled, and questions of medication compliance are not addressed. In addition, it is difficult to compare results between studies because so many different progesterone preparations are used. The use of progesterones for the treatment of mastodynia remains controversial, but commonly practiced in some settings.

The current study employs a validated survey instrument to measure the prevalence and severity of breast pain in women receiving long-term progesterone supplementation for contraception. These results will be compared with those of an age-matched control population. When completed, this cross-sectional study will: 1) provide evidence for or against a role for progesterones in the treatment and prevention of mastodynia, 2) estimate the impact of mastodynia on productivity and readiness in our active duty servicewomen, and 3) provide some insight into current perceptions of the quality of medical care available for mastodynia patients.

METHODS

General Study Design

Women between the ages of 18 and 44 years, receiving Depo-Provera® injections for contraception, were enrolled at 11 OB/GYN or Family Medicine clinics evenly distributed across the United States. An informed consent form was required because demographic data was retained on these women. Approximately 30 days following Depo-Provera® administration the study instrument was mailed to the volunteers. If the completed questionnaire was not received within 30 days, a second, and then a third questionnaire was sent. Only questionnaires that were completed within 90 days of the Depo-Provera® injection were retained. Age-matched controls (+/- 6 months) were randomly selected by Michigan-based Vector Research, and current addresses were appended from the Defense Information System Database (DMIS) in Monterey, California. Questionnaires were mailed to control subjects in three large batches.

Questionnaire Design and Validation

The questionnaire was designed to record and quantify recent episodes of breast pain. A breast pain severity score is calculated based on intensity of the pain (visual analog scale), duration of the pain, disruption of activities of daily living and requirement for medication. The questionnaire distinguishes cyclic from non-cyclic mastodynia and queries satisfaction with medical evaluation and treatment. Confounding variables are accounted for with questions concerning hormonal medication usage, variations in body size, early or surgical menopause, pregnancy or lactation, and recent breast surgery. The questionnaire also contains several question repeats to document internal consistency.

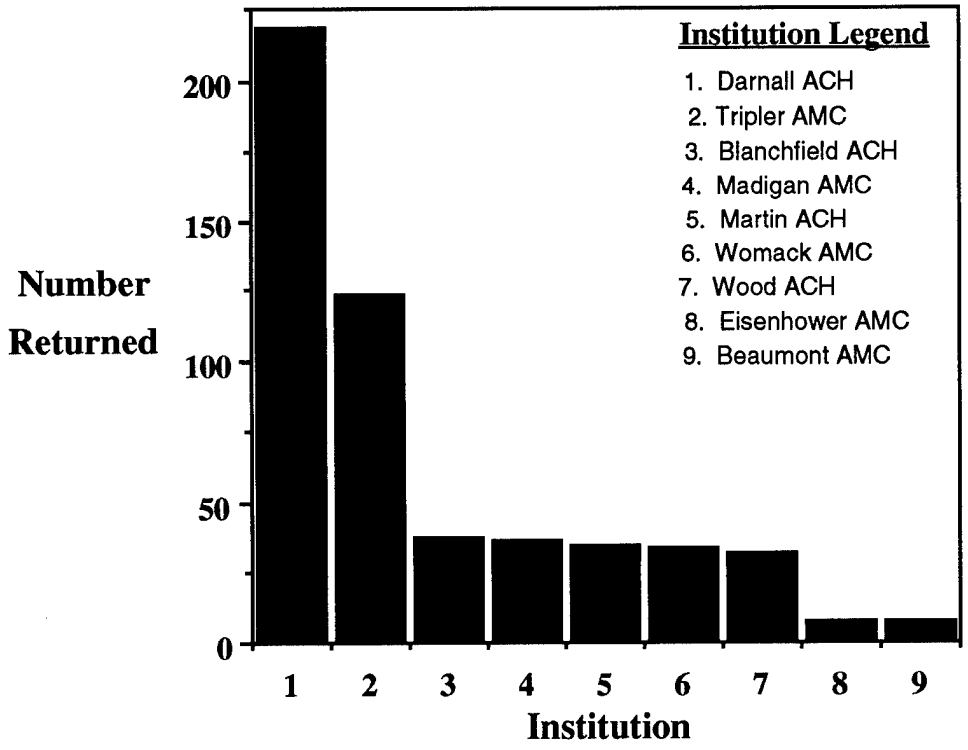
The questionnaire was developed and refined in the breast clinic at Tripler Army Medical Center. At the time of this writing the questionnaire, in its final form, has been administered to 68 women in this clinic who have subsequently been interviewed and examined by the P.I. The calculation of the breast pain severity score continues to undergo some refinement.

RESULTS

Analysis of survey data for the treatment and control groups awaits completion of accrual. Health care providers in a total of 15 clinics had initially expressed interest in participating in the study, but the rigors of the human use review process eliminated four of these. At the time of this writing, the survey has been formatted for automated reading on

a Scantron 8200® optical mark reader, and databases have been developed using Excel and SAS. The survey instrument has been approved by the Army Personnel Survey Office, nine institutional human use committees and the Office of the Surgeon General. Eleven OB/GYN or Family Medicine clinics across the United States are actively accruing Depo-Provera® patients. Treatment arm enrollment has reached 1,300 and, thus far, 533 volunteers have returned completed questionnaires for a return rate of 41%. A breakdown of completed questionnaires returned by institution is provided in figure 1. Control arm accrual is currently underway. At the time of this writing questionnaires have been mailed to 3,449 age-matched control subjects.

Figure 1:
Completed Questionnaires by Institution



CONCLUSIONS

Detailed analysis of the data currently being collected will provide important information about the prevalence of cyclic and non-cyclic mastodynia and will either support or refute a role for progesterones in the treatment of this condition.

Thus far this project has demonstrated a unique cooperation between medical specialties (general surgery, gynecology and family medicine) and between widely separated medical treatment facilities. The problems of age-matching and selection of a randomized control population have been addressed and the logistics of rapid transfer of large blocks of data have been simplified.

REFERENCES

[1]Hinton CP, Bishop HM, Holliday HW, Doyle PJ, Blamey RW. A double-blind controlled trial of danazol and bromocriptine in the management of severe cyclical breast pain. British J Clin Pract 1986; 40: 326 - 330.

[2]Pye JK, Mansel RE, Hughes LE. Clinical experience of drug treatments for mastalgia. Lancet Aug 17, 1985; 313-317.

[3]Kuttenn F, Fournier S, Sitruk-Ware R, Martin P, Mauvais-Jarvis P. Progesterone insufficiency in benign breast disease. In, Endocrinology of Cystic Breast Disease. Edited by Angeli A, Bradlow HL, Dogliotti L. Raven Press, NY. pp 230 - 252.

[4]Ibid.

[5]Walsh PV, Morris K, McDicken IW, Whitehouse GH, George WD. Luteal phase function and benign breast disease. In, Benign Breast Disease, (Baum, M, Ed.) Royal Society of Medicine International Congress and Symposia, Series No. 76. The Royal Society of Medicine. pp 53 - 59.

[6]Ibid, Gorins A, Thierree R, Sauval P. Hormonal profile of benign breast disease and premenstrual mastodynia.

[7]Sitruk-Ware R, Sterkers N, Mauvais-Jarvis P. Inadequate corpus luteum function in women with benign breast diseases. J Clin Endocrinol Metab 1977; 771-774.

[8]Sitruk-Ware R, Sterkers N, Mauvais-Jarvis P. Benign breast disease. I. Hormonal investigation. 1979; Obstet Gynecol; 457 - 460.

[9]Kuttenn F, Fournier S, Sitruk-Ware R, Martin P, Mauvais-Jarvis P. Progesterone insufficiency in benign breast disease. In, Endocrinology of Cystic Breast Disease. Edited by Angeli A, Bradlow HL, Dogliotti L. Raven Press, NY. pp 230 - 252.

[10]Mauvais-Jarvis P, Sterkers N, Kuttan F and Beauvais J. Traitment des mastopathis benignes par la progesterone et les progestatifs. J Gynecol Obstet Biol Reprod (Paris) 1978; 7: 477-484.

[11]Cupceancu B. Combined tamoxifen-lynestrenol treatment in benign breast disease. Rev Roum Med - Endocrinol 1985; 23: 265 - 272.

[12]Uzan S, Denis C, Pomi V, Varin C. Double-blind trial of promegestone (R5020) and lynestrenol in the treatment of benign breast disease. Eur J Obstet Gynecol Reprod Biol 1992; 43: 219 - 227.

[13]Kubista E, Muller G, Spona J. Treatment of mastopathies with cyclic mastodynia. Clinical results and hormone profiles. Rev Fr Fynecol Obstet (FRANCE) 1987; 82: 221-7.

[14]Lotze W. Therapy of mastodynia and simple mastopathy. Zentralbl Gynakol (Germany) 1990; 112: 1151-5.

---

[15]McFadyen IJ, Raab GM, Macintyre CCA, Forrest APM. Progesterone cream for cyclic breast pain. Br Med J 1989; 298: 931.

[16]Nappi C, Affinito P, Di Carlo C, Esposito G, Montemagno U. Double-blind controlled trial of progesterone vaginal cream treatment for cyclic mastodynia in women with benign breast disease. J Endocrinol Invest 1992; 15: 801 - 806.

[17]Maddox PR, Harrison BJ, Horobin JM, Walker K. A randomized controlled trial of medroxyprogesterone acetate in mastalgia. Ann Roy Coll Surg Eng 1990; 72: 71-76.